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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/14	A1	(11) International Publication Number: WO 97/23479
		(43) International Publication Date: 3 July 1997 (03.07.97)

(21) International Application Number: PCT/US96/20599

(22) International Filing Date: 20 December 1996 (20.12.96)

(30) Priority Data:
60/009,098 22 December 1995 (22.12.95) US

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(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NOVEL SYNTHESIS

(57) Abstract

The present invention relates to a novel method for synthesizing imidazole derivatives having 4-aryl, 5-pyrimidine heterocyclic rings using a novel cycloaddition reaction.

Atty. Docket No. 3015/6/US
Serial No. 10/021,780
Anantanarayan et al.
Reference 23 of 77

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Novel Synthesis

Field of the Invention:

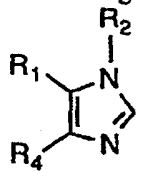
The present invention relates to a novel method for synthesizing imidazole derivatives having 4-aryl, 5-pyrimidine heterocyclic rings.

Background of the Invention:

The present invention describes a novel, and general method to prepare 5-pyrimidinyl substituted imidazoles. Previous syntheses of this class of molecules utilized the van Leusen reaction (van Leusen, A.M., et. al. *J. Org. Chem.* **1977**, *42*, 1153), which involves the cycloaddition of an imine and a tosylisonitrile. Difficulties in preparing the aldehyde precursors to the desired imines limited the scope of this approach. In Adams et al., WO 95/02591 an improvement on the cycloaddition reaction is shown for similar compounds. However addition of a pyrimidine ring in an environmentally favourable and commercially feasible manner is still needed. The present invention employs a novel method of cycloaddition of a tosylisonitrile with an α-ketoaldimine to produce a 5-keto imidazole derivative. The 5-keto group serves as an excellent precursor for addition of the optionally substituted pyrimidine ring.

Summary of the Invention:

The present invention is to a process of making compounds of Formula (I),



(I)

wherein

R_1 is an optionally substituted pyrimidin-4-yl ring;

R_4 is an optionally substituted phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl ring;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

R_2 is -$(CR_{10}R_{20})_{n'}$ OR_9, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$,

$(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, $-C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9;

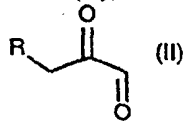
R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl; and

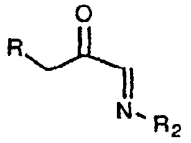
R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

which process comprises:

a) reacting a compound of formula (II), as defined below

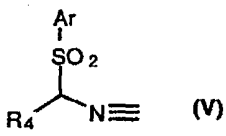

(II)

wherein R is the optional substituent on the pyrimidinyl (R_1) moiety in Formula (I), or is hydrogen, an optionally substituted alkyl or an optionally substituted aryl, with a compound of the Formula R_2NH_2 (III), wherein R_2 is as defined for Formula (I), to yield a compound of Formula (IV)

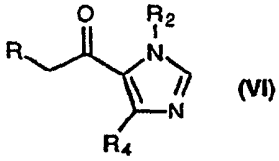

(IV)

wherein R and R_2 are as defined above; and

b) reacting a compound of Formula (IV) with a compound of Formula (V) and a suitable base,

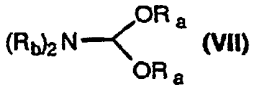

(V)

wherein Ar is an optionally substituted aryl; and R_4 is as defined for Formula (I); to yield a compound of Formula (VI)


(VI)

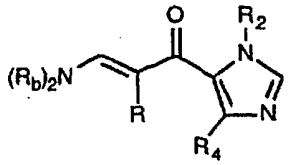
wherein R, R_2 and R_4 are as defined above; and

c) reacting a compound of Formula (VI) with a compound of Formula VII


(VII)

wherein R_a is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl group all of which may be optionally substituted; and R_b

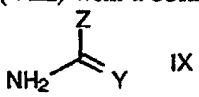
is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl group all of which may be optionally substituted; to yield a compound of Formula (VIII)



(VIII)

wherein R_b is as defined above for Formula (VII), R is as defined above, and R_2 and R_4 are defined as for Formula (I);

d) reacting a compound of Formula (VIII) with a compound of Formula (IX)



IX

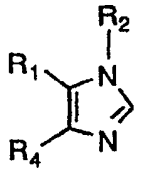
wherein
Z is $N(R^d)_2$, SR^c, OR^c, or R^d.
R^d is independently hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl;
R^c is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl; and
Y is O, S, or NH;
to yield a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention are the novel compounds of Formula (VI), and (VIII) as defined herein.

Detailed Description of the Invention:

The present invention relates to a novel synthesis of a group of imidazole compounds, whose general structure is shown above in Formula (I) above, and further as described in Adams et al., WO 95/02591; Adams et al., WO 96/21452, published 18 July 1996; Adams et al., WO 96/21654, published 18 July 1996; and Adams et al., Attorney Docket No. P50347-2, USSN 08/659,102 filed 3 June 1996; whose disclosures are all incorporated herein by reference.

Preferred compounds of Formula (I) have the structure:



(I)

wherein

R_1 is pyrimidin-4-yl which ring is optionally substituted with one or two substituents each of which is independently selected from optionally substituted C_{1-10} alkyl, optionally substituted aryl, halogen, hydroxyl, thiol, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, CH_2OR_{12}, amino, mono or di-C_{1-10} alkyl substituted amino, NHR_{21}, $N(R_{10})C(O)R_a$ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_4 is an optionally substituted phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl ring;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R8;

R6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R9 is hydrogen, -C(Z)R11 or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9;

R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl; and

R_{21} is alkyl, aryl, arylC_{1-6}alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6}alkyl, wherein each of these moieties may be optionally substituted;

or a pharmaceutically acceptable salt thereof.

Preferably, for compounds wherein R4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, the rings ares optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, -C(Z)NR7R17, -C(Z)OR16, $-(CR_{10}R_{20})_vCOR_{12}$, -SR5, -SOR5, -OR12, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, -ZC(Z)R12, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $-C(Z)NR_{13}R_{14}$, -C(Z)OR3, $-(CR_{10}R_{20})_{m''}COR_3$,

-S(O)$_m$R$_3$, -OR$_3$, halo-substituted-C$_{1-4}$ alkyl, -C$_{1-4}$ alkyl, -(CR$_{10}$R$_{20}$)$_{m''}$NR$_{10}$C(Z)R$_3$, -NR$_{10}$S(O)$_{m'}$R$_8$, -NR$_{10}$S(O)$_{m'}$NR$_7$R$_{17}$, -ZC(Z)R$_3$ or -(CR$_{10}$R$_{20}$)$_{m''}$NR$_{13}$R$_{14}$.

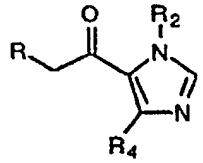
Suitably, wherein R$_5$ is hydrogen, C$_{1-4}$ alkyl, C$_{2-4}$ alkenyl, C$_{2-4}$ alkynyl or NR$_7$R$_{17}$, excluding the moieties -SR$_5$ being -SNR$_7$R$_{17}$ and -SOR$_5$ being -SOH.; v is 0, or an integer having a value of 1 or 2; and m'' is 0, or an integer having a value of 1 to 5.

Suitably, wherein R$_7$ and R$_{17}$ are each independently selected from hydrogen or C$_{1-4}$ alkyl or R$_7$ and R$_{17}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR$_{15}$.

Suitably, R$_{15}$ is R$_{10}$ or C(Z)-C$_{1-4}$ alkyl, and R$_{10}$ and Z are as defined for Formula (I).

The compounds of Formula (I) may be used in association with the treatment of cytokine mediated diseases in a mammal, or for the veterinary treatment of mammals who are in need of inhibition of cytokine production.

Another embodiment of the present invention are the novel compounds of the Formula (VI) having the structure:



(VI)

wherein

R is optionally substituted C$_{1-10}$ alkyl, optionally substituted aryl, halogen, hydroxyl, thiol, C$_{1-10}$ alkoxy, C$_{1-10}$ alkylthio, C$_{1-10}$ alkylsulfinyl, CH$_2$OR$_{12}$, amino, mono or di-C$_{1-6}$ alkyl substituted amino, NHR$_{21}$, N(R$_{10}$)C(O)R$_a$ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR$_{15}$;

R$_a$ is hydrogen, C$_{1-6}$ alkyl, C$_{3-7}$ cycloalkyl, aryl, arylC$_{1-4}$ alkyl, heteroaryl, heteroarylC$_{1-4}$alkyl, heterocyclyl, or heterocyclylC$_{1-4}$ alkyl;

R$_4$ is an optionally substituted phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl ring;

R$_2$ is -(CR$_{10}$R$_{20}$)$_{n'}$ OR$_9$, heterocyclyl, heterocyclylC$_{1-10}$ alkyl, C$_{1-10}$alkyl, halo-substituted C$_{1-10}$ alkyl, C$_{2-10}$ alkenyl, C$_{2-10}$ alkynyl, C$_{3-7}$ cycloalkyl, C$_{3-7}$cycloalkylC$_{1-10}$ alkyl, C$_{5-7}$ cycloalkenyl, C$_{5-7}$cycloalkenyl-C$_{1-10}$-alkyl, aryl,

arylC1-10 alkyl, heteroaryl, heteroaryl-C1-10-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10

n' is 0, or an integer having a value of 1 to 10;

m' is an integer having a value of 1 or 2,

Z is oxygen or sulfur;

R_9 is hydrogen, $-C(Z)R_{11}$ or optionally substituted C1-10 alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C1-4 alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C1-4 alkyl;

R_{11} is hydrogen, C1-10 alkyl, C3-7 cycloalkyl, heterocyclyl, heterocyclyl C1-10alkyl, aryl, arylC1-10 alkyl, heteroaryl or heteroarylC1-10 alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C1-4 alkyl, optionally substituted aryl or optionally substituted aryl-C1-4 alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

R_{15} is R_{10} or C(Z)-C1-4 alkyl;

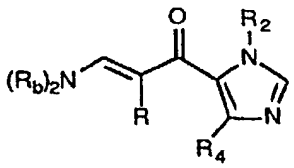
R_{16} is C1-4 alkyl, halo-substituted-C1-4 alkyl, or C3-7 cycloalkyl;

R_{18} is C1-10 alkyl, C3-7 cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C1-10alkyl, heteroaryl or heteroarylalkyl;

R_{19} is hydrogen, cyano, C1-4 alkyl, C3-7 cycloalkyl or aryl; and

R_{21} is alkyl, aryl, arylC1-6alkyl, heterocyclic, heterocyclylC1-6 alkyl, heteroaryl, heteroarylC1-6alkyl, wherein each of these moieties may be optionally substituted.

Yet another embodiment of the present invention are the novel compounds of Formula (VIII) having the structure:



(VIII)

wherein

R_b is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl, all of which may be optionally substituted;

R is optionally substituted alkyl, optionally substituted aryl, 1-4 alkyl, halogen, hydroxyl, thiol, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono or di-C_{1-6} alkyl substituted amino, NHR_{21}, $N(R_{10})C(O)R_a$ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R4 is an optionally substituted phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl ring;

R_2 is $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10

n' is 0, or an integer having a value of 1 to 10;

m' is an integer having a value of 1 or 2,

Z is oxygen or sulfur;

R_9 is hydrogen, $-C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

R_{15} is R_{10} or $C(Z)$-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

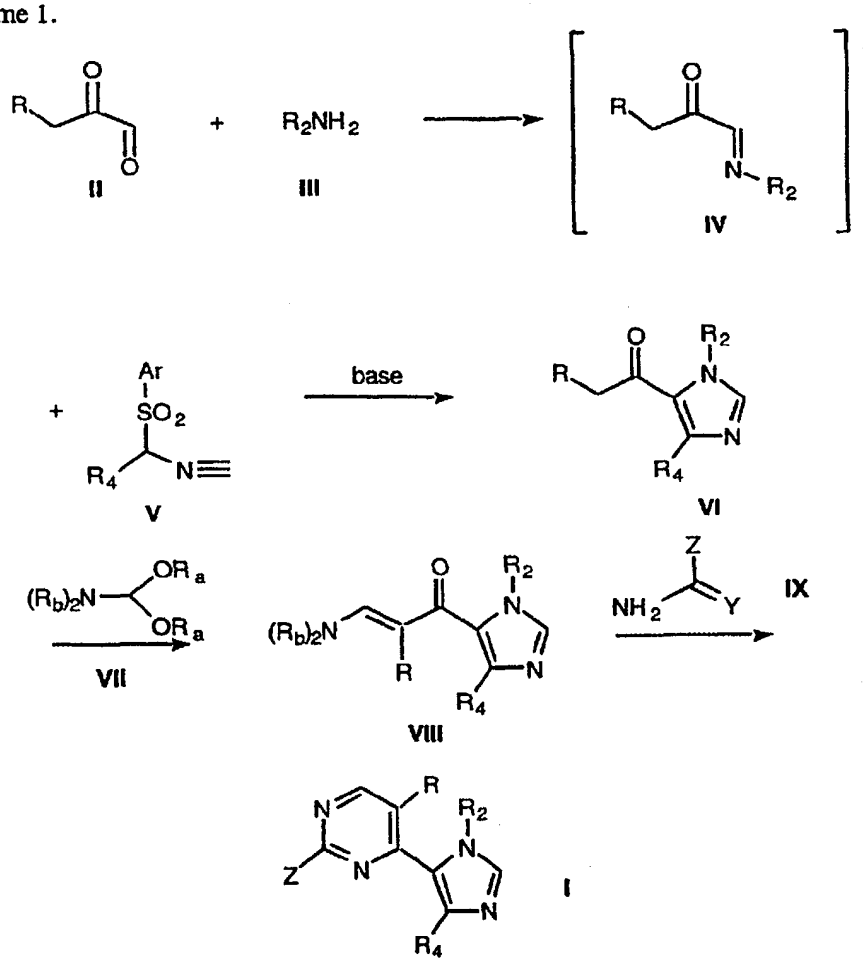
R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

R_{21} is C_{1-6} alkyl, aryl, arylC_{1-6}alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6}alkyl, wherein each of these moieties may be optionally.

Unles otherwise defined in any of the references incorporated herein, the term "optionally substituted" as used herein shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; S(O)m alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; or where the R_7R_{17} may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C_{1-10} alkyl, such CF_2CF_2H, or CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_m$ alkyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; alkyl, or CF_3.

A general method of synthesis for compounds of Formula (I) is shown below Scheme 1.



Scheme 1

The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) having a variety of different R_1, R_2, and R_4 groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the imidazole nucleus has been established, further compounds of Formula (I) may be prepared by applying standard techniques for functional group interconversion, well known in the art. For instance, on the pyrimidine ring, halogen from OH, by reacting with POX_3 or PX_3, wherein X is halogen; C_{1-4} alkylsulfinyl from C_{1-4} alkylthio by oxidation of the sulfur with an appropriate oxidant; $N(R_{10})C(O)R_a$ from $NH(R_{10})$ by acylation on nitrogen with

an appropriate acylating agent; $YC(O)R_a$ where Y is any leaving group. For other alternative groups on the R_2 or R_4 moiety, such as $-C(O)NR_{13}R_{14}$ from $-CO_2CH_3$ by heating with or without catalytic metal cyanide, e.g. NaCN, and $HNR_{13}R_{14}$ in CH_3OH; $-OC(O)R_3$ from -OH with e.g., $ClC(O)R_3$ in pyridine; $-NR_{10}-C(S)NR_{13}R_{14}$ from $-NHR_{10}$ with an alkylisothiocyante or thiocyanic acid; $NR_6C(O)OR_6$ from $-NHR_6$ with the alkyl chloroformate; $-NR_{10}C(O)NR_{13}R_{14}$ from $-NHR_{10}$ by treatment with an isocyanate, e.g. HN=C=O or $R_{10}N=C=O$; $-NR_{10}-C(O)R_8$ from $-NHR_{10}$ by treatment with Cl-$C(O)R_3$ in pyridine; $-C(=NR_{10})NR_{13}R_{14}$ from $-C(NR_{13}R_{14})SR_3$ with $H_3NR_3^+OAc^-$ by heating in alcohol; $-C(NR_{13}R_{14})SR_3$ from $-C(S)NR_{13}R_{14}$ with R_6-I in an inert solvent, e.g. acetone; $-C(S)NR_{13}R_{14}$ (where R_{13} or R_{14} is not hydrogen) from $-C(S)NH_2$ with $HNR_{13}R_{14}$-$C(=NCN)$-$NR_{13}R_{14}$ from $-C(=NR_{13}R_{14})$-SR_3 with NH_2CN by heating in anhydrous alcohol, alternatively from $-C(=NH)-NR_{13}R_{14}$ by treatment with BrCN and NaOEt in EtOH; $-NR_{10}-C(=NCN)SR_8$ from $-NHR_{10}$ by treatment with $(R_8S)_2C=NCN$; $-NR_{10}SO_2R_3$ from $-NHR_{10}$ by treatment with $ClSO_2R_3$ by heating in pyridine; $-NR_{10}C(S)R_3$ from $-NR_{10}C(O)R_8$ by treatment with Lawesson's reagent [2,4-*bis*(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; $-NR_{10}SO_2CF_3$ from $-NHR_6$ with triflic anhydride and base wherein R_3, R_6, R_{10}, R_{13} and R_{14} are as defined in Formula (I) herein.

Precursors of the groups R_1, R_2 and R_4 can be other R_1, R_2 and R_4 groups which can be interconverted by applying standard techniques for functional group interconversion. For example a compound of the formula (I) wherein R_2 is halo-substituted C_{1-10} alkyl can be converted to the corresponding C_{1-10} alkylN_3 derivative by reacting with a suitable azide salt, and thereafter if desired can be reduced to the corresponding C_{1-10}alkylNH_2 compound, which in turn can be reacted with $R_{18}S(0)_2X$ wherein X is halo (e.g., chloro) to yield the corresponding C_{1-10}alkyl$NHS(0)_2R_{18}$ compound.

Alternatively a compound of the formula (I) wherein R_2 is halo-substituted C_{1-10}-alkyl can be reacted with an amine $R_{13}R_{14}NH$ to yield the corresponding C_{1-10}-alkyl$NR_{13}R_{14}$ compound, or can be reacted with an alkali metal salt of $R_{18}SH$ to yield the corresponding C_{1-10}alkylSR_{18} compound.

In Scheme I the compounds of Formula (I) are suitably prepared by reacting a compound of the Formula (II) with a compound of the Formula (III) wherein R is any suitable group, such as H, alkyl, substituted alkyl, aryl, aryl alkyl, heterocyclic, heterocylic alkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or amino, and R_2 is as defined herein, for Formula (I), or is a precursor of the group R_2, and thereafter if necessary converting a precursor of R_2 to the desired R_2 group. Suitable precursor groups of R_2 include

various well known protecting groups, particularly when R_2 is a nitrogen containing heterocyclic ring, such as piperidine. Suitable protecting groups are described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. When R_2 is an optionally substituted cycloalkyl, such as a 4-hydroxy-cyclohexyl, the precursor cyclohexanone could be used, and then reduced to the alcohol.

The compounds of Formula (IV) which are formed are either isolated, or more suitably reacted in situ with compounds of the Formula (V) and a suitable base, where Ar is an optionally substituted phenyl group and R_4 is defined herein, for compounds of Formula (I), to produce compounds of the Formula (VI). Heating compounds of the Formula (VI) with an enaminating reagent such as a compound of Formula (VII), or derivatives thereof, such as reagents of similar structure and reactivity to DMFDMA which include tris(dimethylamino)methane or tert-butoxybis(dimethylamino)-methane, or any other reactive species known to behave as enaminating agents; which produces compounds of the Formula (VIII), which can be isolated, or more preferably reacted in situ with reagents of Formula (IX), where Y and Z are defined for Formula (IX) above to produce the compounds of Formula (I).

An alternative to using reagents of Formula (VII) to produce an enamine of Formula (VIII) is to react compounds of Formula (VI) with formylating agents, such as formate esters, or formamides, to produce 1,3-dicarbonyl compounds which, when in their tautomeric form, are similar to compounds of the Formula (VIII), where $(R_b)_2N$ = OR, wherein R is alkyl, alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, heterocyclicalkyl, or silyl. Compounds of the Formula (VIII), where $(R_b)_2N$ = OR can be reacted directly with reagents of the Formula (IX) to produce compounds of the Formula (I).

The process is exemplified, in Scheme I, by reaction of pyruvaldehyde (Formula II, R = H), which is typically obtained as an aqueous solution, with a primary amine (Formula III) in a solvent to produce imines of the Formula (IV), employing a modification of the method of van Koten (see van der Poel and van Koten, *Synth. Commun.* **1978**, *8*, 305 whose disclosure is incorporated by reference herein in its entirety). Suitable solvents for this process include, but are not limited to, ethereal solvents, such as tetrahydrofuran (THF), t-butyl methyl ether (TBME), diethyl ether, acetonitrile (MeCN), ethyl acetate (EtOAc), N,N,-dimethylformamide (DMF), and dimethylsulfoxide (DMSO). The reaction

requires times of ~1 min to about 24 h, with the preferred times being from about 10-20 min. The reaction is suitably conducted at temperatures ranging from about 0 °C to room temperature, or may be performed at elevated temperatures, of at least 100 °C, if so desired.

Imines of Formula (IV) can be dissolved in a solvent and reacted with compounds of Formula (V), with or without added base, to produce compounds of Formula (VI). A suitable base for this reaction is potassium carbonate, or those noted below and suitable solvents include DMF and DMSO as noted below. The reaction can be conducted at 0 °C, room temperature or as high as about 65°C.

A further embodiment of the present invention involves the preparation of the imines of the Formula (IV) *in situ*, followed by reaction with isonitriles of the Formula (V) to produce imidazoles of the Formula (VI). In this process, aldehydes of Formula (II) are combined with primary amines of Formula (III) in a suitable solvent, and after the prescribed amount of time the imine formation is considered complete and isonitriles of the Formula (V) and a suitable base are added. Suitable solvents include, but are not limited to, acetonitrile, THF, MeCN, toluene, EtOAc, DMF, and DMSO and mixtures thereof. The imine formation requires times of ~5 min to about 6 hours, with the preferred times being about 10-20 min and can be conducted at temperatures ranging from about 0 °C to 60 °C. After addition of the isonitrile, the reaction typically requires an additional 2 to 24 hours at temperatures of 0 °C to 65 °C to go to completion. The reaction proceeds without bases or in the presence of suitable bases, including but not limited to including inorganic and organic amine bases, such as potassium carbonate, sodium carbonate, K_3PO_4, K_2HPO_4, Na_2HPO_4, including inorganic and organic amine bases, such as secondary amines, e.g. morpholine, pyrrolidine, piperidine, and tertiary amines, such as DBU or DBM, as well as tetramethyl guanidine.

Imidazoles of the Formula (VI) can be converted to compounds of the Formula (VIII) by the action of agents of the Formula (VII), or agents of similar structure and reactivity. The process involves heating compounds of Formula (VI) with N,N-dimethylformamide dimethyl acetal (DMFDMA) with no solvent, or a suitable solvent, at temperatures higher than about 70 °C. Suitable solvents include, but are not limited to toluene, ethanol, 1-propanol, 2-propanol, DMF, and DMSO. Reagents of similar structure and reactivity to DMFDMA include tris(dimethylamino)methane or tert-butoxybis(dimethylamino)methane, or other

reactive species know to behave as enaminating agents. With some of the more reactive enaminating reagents, the temperature for this process can be lower than the 70 °C mentioned above.

Compounds of the Formula (VIII) can be isolated, or prepared in situ, and reacted further as shown in Scheme 1. In either case, the reaction involves reacting compounds of Formula (VIII) with compounds of Formula (IX) in a suitable solvent, and a suitable base, if necessary. Suitable solvents include, but are not limited to, alcohols, such as methanol, ethanol, 1-propanol and 2-propanol, toluene, alone or in combination with an alcohol, DMF, DMSO, or combinations of the above. Reagents of the Formula (IX), when Y is NH, are typically obtained as an acid salt, and as such, require the action of a base to react with compounds of the Formula (VIII). When Y is O or S, the reaction may require either acid or base catalysis. Suitable bases include, but are not limited to, NaOMe, NaOEt, potassium carbonate, and KOH. Temperatures of about 25 to about 110 °C have been found to be useful for this conversion, with temperatures > 65 °C being preferred.

A further embodiment of the present invention involves the preparation of imidazoles of the Formula (I) as shown in Scheme 1 in a single pot. The reaction conditions mentioned above are generally suitable for conducting the synthesis in one pot, with one modification. The conversion of compounds of the Formula (VI) to compounds of the Formula (VIII) requires anhydrous conditions. Water is introduced into the reaction when using pyruvaldehyde (II, R = H) as it is sold as a solution in water, which must be removed before proceeding. Following complete conversion of (IV) and (V) to form (VI), suitable methods of dehydration include, but are not limited to the following: using excess DMFDMA (~ 10 equivalents) to both react with water and then with ketones (VI); azeotropically removing water with cosolvents such as toluene, or alcohols; adding other drying agents such as MgSO4; or triethyl orthoformate.

SYNTHETIC EXAMPLES

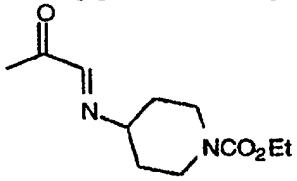
The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom

bombardment, unless otherwise indicated. ^{1}H-NMR (hereinafter "NMR") spectra were recorded at 300 MHz using a Bruker AM 300 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant. Flash chromatography is generally run over Merck Silica gel 60 (230 - 400 mesh).

Example 1

Ethyl 4-(2-oxopropylidene)amino-1-piperidinecarboxylate

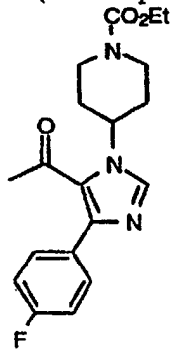


To a solution of pyruvaldehyde (40% w/w solution in water, 2.67 mL, 3.15 g, 17.5 mmol) in 50 mL of Et_2O at room temperature was added dropwise ethyl 4-amino-piperidinecarboxylate (3.0 mL, 3.01 g, 17.5 mmol). After 20 min, the solution was diluted with 50 mL of Et_2O and washed with 3 X 30 mL of water. The solution was concentrated in vacuo to yield 2.3 g (58%) of the imine product which was used as such in the subsequent step: ^{1}H NMR ($CDCl_3$) δ 7.58 (1H, s), 4.07 (2H, q, J = 7.1 Hz)), 4.04 (2H, m), 3.39 (1H, m), 3.02 (2H, m), 2.31 (3H, s), 1.65 (4H, m), 1.19 (3H, t, J = 7.1 Hz).

Example (Ia): Alternative conditions utilized in above noted synthesis include MeCN as solvent and mixing the reagents at 0 °C.

Example 2

1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole :



To a solution of the imine described in Example 1 above (1.12 g, 4.95 mmol) in 9 mL of DMF at room temperature was added α-(p-toluenesulfonyl)-4-fluorobenzylisonitrile (1.30 g, 4.50 mmol) and K_2CO_3 (0.68 g, 4.95 mmol). After 22 h, the solution was diluted with 75 mL of EtOAc and washed with 2 X 60 mL of 3 N HCl. The aqueous layers were combined and basified with excess solid K_2CO_3 until the bubbling ceased. The aqueous layer was transferred to a separatory funnel and extracted 2 x 75 mL of EtOAc. The combined organics were washed with 3 X 50 mL of water and concentrated in vacuo. The residue was recrystallized from $CHCl_3$/Hexane to yield the imidazole product (1.05 g, 65%) which was used in subsequent steps: mp = 118-19 °C; IR (KBr) 1691, 1681, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (1H, s), 7.44 (2H, m), 7.14 (2H, t, J = 8.6 Hz), 5.00 (1H, tt, J = 3.7, 12.1 Hz), 4.35 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 2.93 (2H, m), 2.18 (2H, br d, J = 12.9 Hz), 2.12 (3H, s), 1.80 (2H, dq, J = 4.2, 12.4 Hz), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCL_3$) d 191.00, 164.74, 161.45, 155.31, 149.77, 137.39, 131.46, 131.35, 126.99, 115.63, 115.34, 61.59, 54.85, 43.29, 33.40, 30.45, 14.63; ^{13}C NMR ($CDCl_3$) δ 191.00, 164.75, 161.45, 155.31, 149.77, 137.39, 131.46, 131.35, 126.99, 115.63, 115.35, 61.59, 54.85, 43.29, 33.40, 30.45, 14.63; Anal. Calcd for $C_{19}H_{22}N_3O_3F$: C, 63.5; H, 6.2; N, 11.7. Found C, 63.1; H, 6.1; N, 11.5.

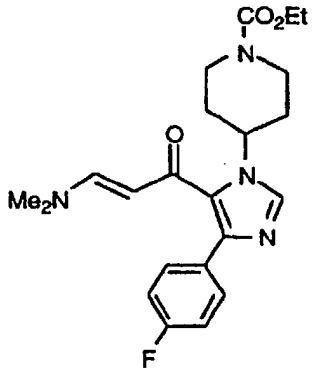
In an alternative procedure to that listed above, the title compound was prepared in the following manner: To a solution of pyruvaldehyde (40% w/w solution in water, 3.97 mL, 4.68 g, 25.94 mmol) in 34 mL of DMSO at room temperature was added dropwise ethyl 4-amino-piperidinecarboxylate (4.45 mL, 4.47 g, 25.94 mmol). After 10 min α-(p-toluenesulfonyl)-4-fluoro-benzylisonitrile (5.0 g, 17.3 mmol) and K_2CO_3 (2.39 g, 17.3 mmol) were added. After 15 h, the solution was diluted with 100 mL of EtOAc and washed with 2 X 100 mL of 3 N HCl. The aqueous layers were combined and basified with excess solid K_2CO_3 until the bubbling ceased. The aqueous layer was transferred to a separatory funnel and extracted 2 x 150 mL of EtOAc. The combined organics were washed with 3 X 75 mL of water and concentrated in vacuo to yield the imidazole product (4.65 g, 75%) which was used as is in subsequent steps.

Alternative conditions for this synthesis include the Examples shown below::

Solvent	Base / eq	Temp for imine formation	Temp for cycloaddition	Imine formation time
DMF	K_2CO_3 / 1.2	room temp.	room temp.	15 min
DMF	K_2CO_3 / 1.1	room temp.	room temp.	15 min
DMF	K_2CO_3 / 1.2	room temp.	room temp.	20 min
DMF	K_2CO_3 / 1.2	room temp.	room temp.	17 min.
DMF	K_2CO_3 / 1.2	room temp.	room temp.	80 min
DMF	K_2CO_3 / 1.2	room temp.	room temp.	75 min
DMF	K_2CO_3 / 1.2	room temp.	room temp.	6 h
DMF	K_2CO_3 / 1.2	room temp.	room temp.	2 h
DMF	K_2CO_3 / 1.1	room temp.	room temp.	85 min
DMF	K_2CO_3 / 1.2	room temp.	room temp.	12 min
DMF	K_2CO_3 / 1.2	45 °C	45 °C	12 min
DMF	K_2CO_3 / 1.2	60 °C	60 °C	14 min
DMF/ $MgSO_4$	K_2CO_3 / 1.2	room temp.	room temp.	12 min
DMF	K_2CO_3 / 1.2	rm temp. to 40 °C, distill	room temp.	12 min
DMF	K_2CO_3 / 1.1	40 °C	40 °C	10 min.
DMF	K_2CO_3 / 1.25	0 °C	room temp.	4 h
DMF	K_2CO_3 / 1.2	0 °C	0 °C	2.33 h
DMF	$NaHCO_3$ / 1.3	room temp.	room temp.	75 min.
MeCN	K_2CO_3 / 1.25	room temp.	room temp.	25 min.
MeCN	K_2CO_3 / 1.2	room temp.	room temp.	5 min.
MeCN	K_2CO_3 / 1.2	room temp.	room temp.	10 min.
MeCN	K_2CO_3 / 1.25	0 °C	room temp.	15 min.
MeCN	K_2CO_3 / 1.2	0 °C	0 °C	145 min.
DMSO	K_2CO_3 / 1.25	room temp.	room temp.	15 min.
THF	morpholine / 3	room temp.	room temp.	1 h
THF	K_2CO_3 / 1.2	0 °C	0 °C	145 min.
Toluene	K_2CO_3 / 1.25	room temp.	room temp.	15 min.
EtOAc	K_2CO_3 / 1.0	room temp.	room temp.	11 min.

Example 3

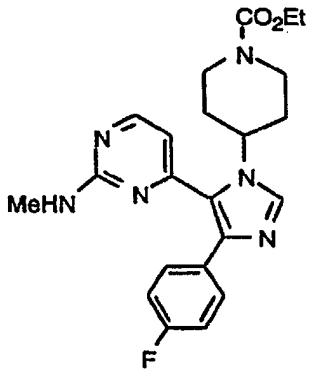
1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(3-N,N-dimethylamino-trans-1-propenone)imidazole



The ketoimidazole prepared in Example 2 above (0.4 g, 1.11 mmol) was dissolved in 4 mL of DMSO and N,N-dimethylformamide dimethyl acetal (0.18 mL, 0.16 g, 1.33 mmol) and was heated at 90 °C for 5.5 h. The solution was cooled to room temperature and the solvents were removed under vacuum by Kugel-Rohr distillation. The residue was purified by preparative TLC using hexanes/ethyl acetate (1:1) and eluting twice to give 0.3 g (65%) of the title compound as a brown solid: ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, s), 7.55 (2H, m), 7.48 (1H, m), 7.02 (2H, t, J = 8.7 Hz), 5.02 (1H, d, J = 12.6 Hz), 4.91 (1H, m), 4.30 (2H, m), 4.13 (2H, q, J = 7.1 Hz), 2.99 (3H, br s), 2.89 (2H, m), 2.51 (3H, br s), 2.18 (2H, d, J = 12.1 Hz), 1.78 (2H, dq, J = 4.3, 12.3 Hz), 1.26 (3H, t, J = 7.1 Hz).

Example 4

1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-{2-(methylamino)-4-pyrimidinyl)imidazole :



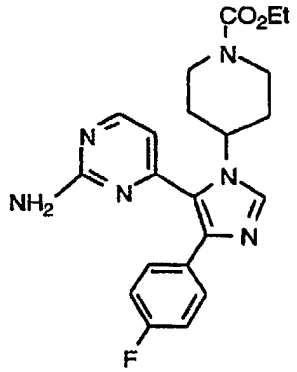
To a solution of the ketoimidazole prepared in Example 2 above (2.1 g,5.85 mmol) in 10.5 mL of 1-propanol was added N,N-dimethylformamide dimethyl acetal (1.32 mL, 1.18 g, 9.94 mmol) and the solution was heated at 100 °C for 6 h. At this time, TLC indicated no starting material and N-methylguanidine•HCl (0.96 g, 8.77 mmol) and NaOEt (21% w/w solution, 3.50 mL, 3.05 g, 9.35 mmol) were added. After 18 hours, the solution was cooled to room temperature, diluted with 40 mL of water, 50 mL of 3N HCl and 50 mL of EtOAC. The layers were separated and the organic layer wash washed again with 20 mL of 3N HCl. The combined aqueous layers were basified with solid K_2CO_3 until bubbling ceased. The aqueous layer was extracted with EtOAc (2 X 50 mL). The combined organics were washed with 3 X 100 mL of water, concentrated and the residue was recrystallized from EtOAc to give 1.24 g (50%) of the title compound: mp = 205-206 °C; IR (KBr) 3242, 3110, 1695, 1588, 1568, 1532, 1507 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (1H, d, J = 5.0 Hz), 7.71 (1H, s), 7.44 (2H, m), 6.97 (2H, t, J = 8.7 Hz), 6.40 (1H, d, J = 5.0 Hz), 5.18 (1H, m), 4.83 (1H, m), 4.34 (2H, m),4.15 (2H, q, J = 7.1 Hz), 3.02 (3H, d, J = 5.0 Hz), 2.81 (2H, m), 2.19 (2H, m), 1.87 (2H, dq, J = 4.4, 12.5 Hz), 1.27 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 164.00, 163.03, 160.73, 158.51, 158.32, 155.31, 141.96, 135.57, 130.52, 130.07, 129.97, 125.01, 115.39, 115.11, 111.73, 61.61, 53.80, 43.42, 33.43, 28.43, 14.63; Anal. Cald for $C_{22}H_{25}N_6O_2F$; C, 62.2; H, 5.9; N, 19.8; Found C, 61.9, H, 6.0; N, 19.4.

Examples 4 (a) and (b) include the alternative conditions :

Solvent	DMFDMA temp	Base	Pyrimidine temp.
EtOH	85 °C	NaOMe	85 °C
DMF	100 °C	NaOMe	65 °C

Example 5

1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-(amino)-4-pyrimidinyl)imidazole :



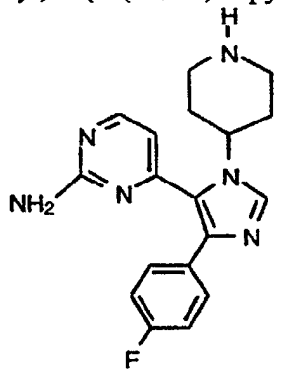
To a solution of the ketoimidazole prepared in Example 2 above (2.6 g, 7.24 mmol) in 15 mL of DMF was added N,N-dimethylformamide dimethyl acetal (1.92 mL, 1.72 g, 14.5 mmol) and the solution was heated at 120 °C for 2 h. At this time, TLC and HPLC indicated no starting material and the solution was cooled to 95 °C and ethanol (30 mL), guanidine•HCl (2.77 g, 28.95 mmol) and K_2CO_3 (4.0 g, 28.9 mmol) were added. After 16 hours, HPLC indicated that the reaction was complete and the solution was cooled to room temperature. The solution was diluted with 100 mL of EtOAc and washed with 2 X 150 mL of 3 N HCl. The aqueous layers were combined and basified with excess solid K_2CO_3 until the bubbling ceased. The aqueous layer was transferred to a separatory funnel and extracted 2 x 150 mL of EtOAc. The combined organics were dried over Na_2SO_4 and activated charcoal, filtered through Celite, and concentrated in vacuo. The residue was recrystallized from EtOAc/MeOH/Hexanes to yield the imidazole product (0.9 g, 30%) as a beige solid: mp = 228-230 °C; IR (KBr) 3321, 3157, 1712, 1658, 1568, 1507, 1470, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (1H, d, J = 5.3 Hz), 7.71 (1H, s), 7.43 (2H, m), 7.00 (2H, t, J = 8.7 Hz), 6.50 (1H, d, J = 5.3 Hz), 5.16 (2H, br s), 4.74 (1H, tt, J = 3.7, 12.0 Hz), 4.35 (2H, m), 4.15 (2H, q, J = 7.1 Hz), 2.82 (2H, t, J = 12.5 Hz), 2.15 (2H, d, J = 12.5 Hz), 1.85 (2H, m), 1.28 (3H, t, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6) δ 163.61, 162.76, 159.54, 158.66, 158.01, 154.35, 138.88, 136.25, 131.00, 129.16, 129.05, 124.98, 115.08, 114.80, 110.84, 60.64, 53.06, 42.70, 32.48, 14.43; Anal. Calcd for $C_{21}H_{23}N_6O_2F$; C, 61.4; H, 5.7; N, 20.5; Found C, 61.0, H, 5.5; N, 20.3.

Examples 5 (a) to (d) include the alternative conditions :

Solvent	DMFDMA temp	Base	Pyrimidine temp.
EtOH	90 °C	NaOMe	80 °C
EtOH	90 °C	NaOMe	85 °C
DMF	120 °C	K_2CO_3/EtOH	95 °C
Toluene	115 °C	K_2CO_3/EtOH/IPA	80-90 °C

Example 6

1-(4-piperidinyl)-4-(4-fluorophenyl)-5-{2-(amino)-4-pyrimidinyl)imidazole



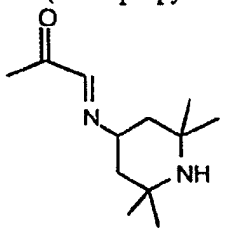
To a solution of the ketoimidazole prepared in Example 2 above (1.4 g, 3.89 mmol) in 5 mL of toluene was added N,N-dimethylformamide dimethyl acetal (1.04 mL, 0.93 g, 7.80 mmol) and the solution was heated at 115 °C for 4 h. At this time, TLC and HPLC indicated no starting material and the solution was cooled to 80 °C and 2-propanol (25 mL), guanidine•HCl (1.49 g, 15.6 mmol) and K_2CO_3 (2.15 g, 15.6 mmol) were added. After 16.5 hours, HPLC indicated that the reaction was 60% complete. Ethanol (20 mL) was added and heating was continued at 90 °C for 24h, at which point HPLC showed none of the aminoenone remaining. AT this point, KOH (2.19 g, 38.9 mmol) and water (10 mL) were added and heating was continued at 95 °C for 8 h. An additional poriton of KOH (2.2 g, 38.9 mmol) was added. After 15 h of heating an additional 4.4 g of KOH was added and heated for 48 h. The solution was cooled to room temperature, diluted with 20 mL of water and the solid which formed was filtered, washed with water (50 mL) and Et_2O (50 mL), and dried to yield 0.44 g (34%) of the title compound as a beige solid: mp = 199-200 °C; IR (KBr) 3471, 3395, 3314, 3167, 1635, 1576, 1566, 1507, 1460 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.20 (1H, d, J = 5.0 Hz), 7.98 (1H, s), 7.43 (2H, m), 7.12 (2H, t, J = 8.9 Hz), 6.81 (2H, br s), 6.41 (1H, d, J = 5.0 Hz), 4.31 (1H, m), 2.97 (2H, d, J = 12.4 Hz), 2.45 (2H, m), 1.86 (2H, m), 1.74 (2H, dq, J = 3.7, 11.8 Hz); ^{13}C NMR (DMSO-d_6) δ 163.67, 162.70, 159.47,

158.68, 158.33, 138.64, 135.79, 130.98, 128.98, 128.88, 125.05, 115.05, 114.77, 110.96, 53.84, 45.39, 34.08; Anal. Calcd for $C_{18}H_{19}N_6F \cdot 0.5\ H_2O$: C, 62.2; H, 5.8; N, 24.2. Found C, 61.9; H, 5.7; N, 23.9.

In an alternative procedure, the substrate was dissolved in 1-PrOH and heated at about 95 °C with DMFDMA, then heated with guanidine•HCl and K_2CO_3 at 95 °C and when the pyrimidine formation was completed, the reaction was heated with excess KOH until product formation was complete.

Example 7

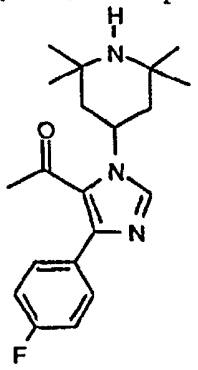
2,2,6,6-Tetramethyl-4-(2-oxopropylidene)aminopiperidine



To a solution of pyruvaldehyde (40% w/w solution in water, 2.68 mL, 3.16 g, 17.5 mmol) in 30 mL of TBME at room temperature was added dropwise 2,2,6,6-tetramethyl-4-amino-piperidine (2.0 mL, 2.19 g, 14.0 mmol). After 30 min, the solution was diluted with 50 mL of TBME and washed with 3 X 25 mL of water and 25 mL of brine. The solution was concentrated in vacuo to yield 2.1 g (71%) of the imine product which was used as such in the subsequent step: ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, s), 3.70 (1H, tt, J = 3.9, 11.6 Hz), 2.34 (3H, s), 1.61 (2H, dd, J = 3.9, 13.0 Hz), 1.32 (2H, t, J = 12.2 Hz), 1.21 (6H, s), 1.14 (6H, s).

Example 8

1-(2,2,6,6-tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole:



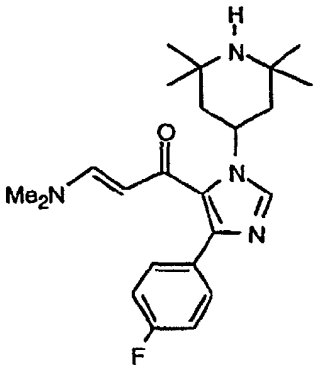
:To a solution of pyruvaldehyde (40% w/w solution in water, 7.56 mL, 8.91 g, 49.5 mmol) in 90 mL of DMSO at room temperature was added dropwise 2,2,6,6-tetramethyl-4-amino-piperidine (9.24 mL, 8.43 g, 65.4 mmol). After 10 min α-(p-toluenesulfonyl)-4-fluorobenzylisonitrile (13.0 g, 44.95 mmol) and K_2CO_3 (7.46 g, 53.95 mmol) were added. After 23 h, the solution was diluted with 250 mL of EtOAc and washed with 2 X 200 mL of 3 N HCl. The aqueous layers were combined and basified with excess solid K_2CO_3 until the bubbling ceased. The aqueous layer was transferred to a separatory funnel and extracted 2 x 250 mL of EtOAc. The combined organics were washed with 3 X 100 mL of water and concentrated in vacuo to yield the title compound (11.6 g, 75%) as a brown oil, which could be recrystallized from $CHCl_3$/hexanes: mp = 134-36 °C; IR (KBR) 3430, 3144, 1659, 1653, 1219 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (1H, s), 7.43 (2H, m), 7.12 (2H, t, J = 8.7 Hz), 5.39 (1H, tt, J = 3.1, 12.5 Hz), 2.11 (3H, s), 2.10 (2H, m), 1.50 (2H, t, J = 12.2 Hz), 1.37 (6H, s), 1.22 (6H, s); ^{13}C NMR ($CDCl_3$) δ 190.77, 164.69, 161.41, 149.79, 137.42, 131.47, 131.36, 127.03, 115.57, 115.29, 52.02, 50.57, 46.20, 34.61, 30.45, 28.06.

Alternative reaction conditions for this synthesis included:

Solvent	Base / eq.	Imine formation temp	Cycloaddition temp.	Imine formation time
DMF	K_2CO_3 / 1.25	room temp.	room temp.	15 min.
DMF/toluene	K_2CO_3 / 1.15	room temp to 65 °C (-H_2O)	room temp.	80 min.
DMF	none	room temp.	room temp.	15 min.
DMF/EtOAc	K_2CO_3 / 1.2	room temp.	room temp.	15 min.
DMSO	K_2CO_3 / 1.25	room temp.	room temp.	20 min.
DMSO/toluene	K_2CO_3 / 1.15	room temp to 55 °C (-H_2O)	room temp.	35 min.
DMSO/ $(MeO)_3CH$	K_2CO_3 / 1.2	room temp to 55 °C (-H_2O)	room temp.	40 min.
DMSO	morpholine/1.3	room temp.	room temp.	15 min.
DMSO	pyrrolidine/1.3	room temp.	room temp.	15 min.
DMSO	K_3PO_4/1.5	room temp.	room temp.	15 min.
DMSO	K_2HPO_4/1.5	room temp.	room temp.	15 min.
DMSO	DBU/1.1	room temp.	room temp.	15 min.
DMSO	Na_2CO_3 / 1.2	room temp	room temp.	15 min.
DMSO	Na_2HPO_4/1.5	room temp.	room temp.	15 min.
DMSO	K_2HPO_4/3.0	room temp.	room temp.	15 min.
DMSO	morpholine/1.05	room temp.	room temp.	18 min.
DMSO	morpholine/1.0	room temp.	room temp.	10 min.
EtOAc	morpholine/1.0	room temp.	room temp.	10 min.
EtOAc	K_2CO_3 / 1.0	room temp	room temp.	12 min.
EtOAc	K_2CO_3 / 1.0	room temp	50 °C	13 min.
EtOAc	K_2CO_3 / 1.0	room temp	35 °C	15 min.
EtOAc	K_2CO_3 / 1.0	room temp	40 °C	15 min.

Example 9

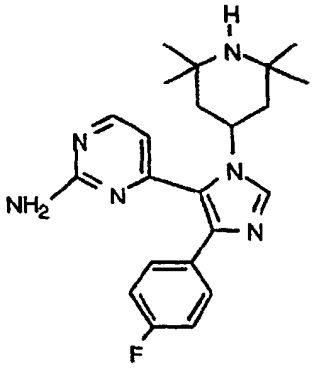
1-(2,2,6,6-tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(3-N,N-dimethylamino-trans-1-propenone)imidazole



The ketoimidazole prepared in Example 8 above (0.75 g, 2.18 mmol) was dissolved in 10 mL of toluene and N,N-dimethylformamide dimethyl acetal (0.43 mL, 0.39 g, 3.28 mmol) and was heated at 115 °C for 20 h. The solution was cooled to room temperature and the solvents were removed under vacuum. The residue was passed through a short plug of silica gel and eluted with EtOAc/MeOH (1:1), and concentrated to give the title compound (0.65 g 76%) of the title compound as a brown solid: ^{1}H NMR ($CDCl_3$) δ 7.65 (1H, s), 7.56 (2H, m), 7.46 (1H, d, J = 12.2 Hz), 7.01 (2H, t, J = 8.8 Hz), 5.32 (1H, m), 5.01 (1H, d, J = 12.6 Hz), 2.96 (3H, br s), 2.48 (3H, br s), 2.09 (2H, dd, J = 3.1, 12.0 Hz), 1.44 (2H, t, J = 12.3 Hz), 1.31 (6H, s), 1.17 (6H, s).

Example 10

1-(2,2,6,6-tetramethyl-4-piperidinyl)-4-(4-fluorophenyl)-5-{2-(methylamino)-4-pyrimidinyl)imidazole



To a solution of the ketoimidazole prepared in Example 8 above (8.0 g,23.3 mmol) in 100 mL of DMSO was added N,N-dimethylformamide dimethyl acetal (6.19 mL, 5.55 g, 46.6 mmol) and the solution was heated at 100 °C for 16 h. At this time, HPLC indicated no starting material and guanidine•HCl (4.45 g, 46.6 mmol) and K_2CO_3 (6.44 g, 46.6 mmol) were added and heating was continued at 100 °C. After 9 hours, the solution was cooled to room temperature, diluted with 100 mL of water, DMSO and MeOH, and filtered. The filtrate was diluted with 200 mL of EtOAc and 400 mL of water. The layers were separated and the aqueous layer was extracted 3 X 200 mL of EtOAc. The organic layers were combined and washed with 3 X 100 mL of water. The organics were washed with 50 mL of brine, dried over Na_2SO_4 and activated charcoal, concentrated and the residue was recrystallized from EtOAc /hexanes to give 3.3 g (36%) of the title compound: mp = 221-22 °C; IR (KBr) 3345, 3319, 3155,1645, 1562 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (1H, d, J = 5.1 Hz), 7.72 (1H, s), 7.45 (2H, m), 7.00 (2H, t, J = 8.7 Hz), 6.49 (1H, d, J = 5.2 Hz), 5.30 (1H, tt, J = 3.2, 12.6 Hz), 5.12 (2H, br s), 2.04 (2H, dd, J = 3.2, 12.4 Hz), 1.48 (2H, t, J = 12.3 Hz), 1.24 (6H, s), 1.17 (6H, s); ^{13}C NMR (DMSO-d_6) δ 163.67, 162.72, 159.49, 158.77, 158.49, 138.68, 135.43, 130.92, 128.93, 128.82, 125.14, 115.09, 114.81, 111.00, 50.81, 48.67, 44.74, 34.06, 28.11. Anal. Calcd for $C_{22}H_{27}N_6F$: C, 66.98; H, 6.90; N, 21.30. Found C, 67.37; H, 6.88; N, 21.39.

Alternative conditions employed include:

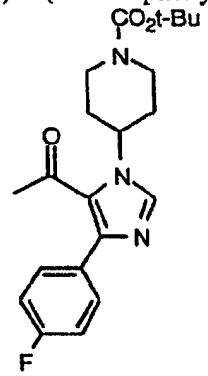
Solvent	DMFDMA temp	Base	Pyrimidine temp.
DMF	100 °C	K_2CO_3	120 °C
DMSO	100 °C	K_2CO_3	100 °C
DMSO	100 °C	KOH	100 °C
1-PrOH	100 °C	KOH/H_2O	100 °C
EtOH	85 °C	NaOMe	85 °C
2-PrOH	85 °C	NaOMe	85 °C

In yet another alternative procedure to those listed above, the title compound was prepared in the following manner: To a solution of pyruvaldehyde (40% w/w solution in water, 5.82 mL, 6.85 g, 38.04 mmol) in 70 mL of DMSO at room temperature was added 2,2,6,6-tetramethyl-4-aminopiperidine (6.52 mL, 5.94 g, 38.04 mmol). After 15-20 min, α-(p-toluenesulfonyl)-4-fluorobenzylisonitrile (10 g, 34.6 mmol) and K_2CO_3 (5.02 g, 36.3 mmol) were added. After 19 h, an HPLC solution assay indicated that 6.79 g (57%) of the ketoimidazole (title compound of

Example 8) had formed and that reaction was complete. To the solution was added 30 mL of toluene, and the solution was heated at 65 °C while the toluene was removed under vacuum. The toluene addition/distillation was repeated two times more. N,N-dimethylformamide dimethyl acetal (DMFDMA) (9.2 mL, 8.24 g, 69.2 mmol) was added and the solution was heated at 100 °C. After 2 h, HPLC indicated no reaction, so an additional 9.2 mL of DMFDMA were added, and after 15 h an additional 5 mL of DMFDMA were added and heated for 1 h. Guanidine•HCl (6.61 g, 69.2 mmol) and K_2CO_3 (9.56 g, 69.2 mmol) were added and heated at 100 °C for 6.75 h, at which point HPLC indicated that the reaction was complete. After cooling to room temperature, the solution was filtered through a pad of Celite, diluted with 250 mL of EtOAc and washed with 4 X 200 mL of 3 N HCl. The aqueous layers were combined and basified with solid KOH to pH = 14. The aqueous layer was transferred to a separatory funnel and extracted 3 x 200 mL of EtOAc. The combined organics were washed with 3 X 100 mL of 3N KOH solution and 50 mL of brine, dried over Na_2SO_4 and activated charcoal, filtered through Celite and concentrated in vacuo. The residue was dissolved in 50 mL of MeOH and the crystals which formed were filtered and washed with 100 mL of EtOAc to yield the title compound (4.89 g, 36%) as a tan solid.

Example 11

1-(1-t-Butoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole

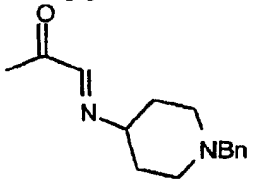


To a solution of t-butyl 4-amino-piperidinecarboxylate (0.95 g, 4.75 mmol) in 40 mL of Et_2O was added pyruvaldehyde (40% w/w solution in water, 0.94 mL, 1.11 g, 6.17 mmol) at room temperature. After 1.75 h, the solution was poured into a separatory funnel, diluted with 30 mL of Et_2O and 10 mL of EtOAc, and washed with 2 X 10 mL of water. The organics were concnetrated in vacuo and the residue was diluted in 10 mL of DMF and α-(p-toluenesulfonyl)-4-fluoro-benzylisonitrile (1.37 g,

4.75 mmol) and K_2CO_3 (0.72 g, 5.23 mmol) were added. After 16 h, the solution was diluted with 100 mL of water and extracted with 2 X 40 mL of EtOAc. The combined organics were washed with 3 X 40 mL of 10% HCl. The aqueous layers were combined and neutralized with excess solid $NaHCO_3$, then basified with 20 mL of 10% KOH. The aqueous layer was transferred to a separatory funnel and extracted 3 x 30 mL of EtOAc. The combined organics concentrated in vacuo to yield the imidazole product (0.5 g, 27%): ^{1}H NMR ($CDCl_3$) δ 7.74, 7.44 (2H, m), 7.13 (2H, t, J = 8.6 Hz), 4.97 (1H, tt, J = 3.7, 12.0 Hz), 4.29 (2H, m), 2.88 (2H, m), 2.15 (2H, m), 2.11 (3H, s), 1.78 (2H, dq, 4.2, 12.2 Hz), 1.48 (9H, s).

Example 12

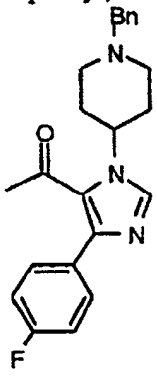
1-Benzyl-4-(2-oxopropylidene)aminopiperidine



To a solution of pyruvaldehyde (40% w/w solution in water, 0.49 mL, 0.57 g, 3.19 mmol) in 10 mL of Et_2O at room temperature was added dropwise 4-amino-1-benzylpiperidine (0.5 mL, 0.46 g, 2.45 mmol). After 20 min, the solution was diluted with 40 mL of Et_2O and washed with 2 X 5 mL of water. The solution was concentrated in vacuo to yield the imine product which was used as such in the subsequent step: ^{1}H NMR ($CDCl_3$) δ 7.62 (1H, s), 7.29 (5H, m), 3.53 (2H, s), 3.28 (1H, m), 2.91 (2H, m), 2.38 (3H, s), 2.15 (2H, m), 1.84 (2H, m), 1.69 (2H, m).

Example 13

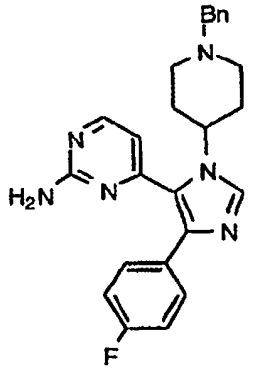
1-(1-Benzyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole



To a solution of the imine described in Example 12 above (assumed 100% yield for Example 12, 0.64 g, 2.44 mmol) in 5 mL of DMF at 0 °C was added α-(p-toluenesulfonyl)-4-fluorobenzylisonitrile (0.85 g, 2.93 mmol) and K_2CO_3 (0.40 g, 2.93 mmol). The solution was stirred at 0 °C for 2 h, then gradually warmed to room temperature over 15 h. The solution was diluted with 70 mL of EtOAc and washed with 100 and 50 mL of water. The organic layer was acidified with 2 X 55 mL of 3N HCl . The aqueous layers were combined and neutalized with solid $NaHCO_3$ then basified with 30 mL of 10% KOH. The aqueous layer was transferred to a separotary funnel, extracted with 2 x 50 mL of EtOAc and concentrated in vacuo to yield the title compound (0.38 g, 41%) which was used in subsequent steps: ^{1}H NMR ($CDCl_3$) δ 7.78 (1H, s), 7.43 (2H, m), 7.27 (5H, m), 7.11 (2H, t, J = 8.6 Hz), 4.80 (1H, tt, J = 3.9, 11.8 Hz), 3.55 (2H, s), 3.02 (2H, d, J = 11.9 Hz), 2.16 (2H, m), 2.10 (3H, s), 1.94 (2H, m).

Example 14

1-(1-Benzyl-4-piperidinyl)-4-(4-fluorophenyl)-5-{2-(amino)-4-pyrimidinyl)imidazole



To a solution of the ketoimidazole prepared in Example 13 above (0.38 g, 1.01 mmol) in 5 mL of EtOH was added N,N-dimethylformamide dimethyl acetal (0.4 mL, 0.36 g, 3.02 mmol) and the solution was heated at 90 °C for 3 h. After 3 h, an additional 1 mL of DMFDMA was added and heated for 3 h. At this time, TLC indicated no starting material and the solution was cooled to 70 °C and guanidine•HCl (0.19 g, 2.02 mmol) and NaOMe (25% w/w solution, 0.46 mL, 0.44 g, 2.02 mmol) were added. After 15 hours, additional N-methylguanidine•HCl (0.19 g, 2.02 mmol) and NaOMe (25% w/w solution, 0.46 mL, 0.44 g, 2.02 mmol) were added and heated at 75 °C for 24 h. The solution was cooled to room temperature, diluted with 50 mL of water and extracted 2 X 50 mL of EtOAC. The combined organics were concentrated and the residue was recrystallized from

EtOAc to give 0.2 g (47%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 8.19 (1H, d, J = 5.2 Hz), 7.76 (1H, s), 7.44 (2H, m), 7.33 (5H, m), 7.01 (2H, t, J = 8.6 Hz), 6.50 (1H, d, J = 5.2 Hz), 5.17 (2H, br s), 4.54 (1H, m), 3.53 (2H, s), 3.02 (2H, m), 2.09 (6H, m).

Additional compounds produced using the analagous methods to those indicated above include:

Example 15: 5-(2-Phenylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole

Example 16: 1-[1-Carboethoxy)piperidin-4-yl]-4-(4-fluorophenyl)-5-[[2-[3-benzyloxy)phenylamino]pyrimdin-4-yl]imidazole

Example 17: 1-[1-Carboethoxy)piperidin-4-yl]-4-(4-fluorophenyl)-5-[[2-[4-benzyloxy)phenylamino]pyrimdin-4-yl]imidazole

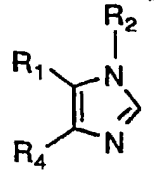
Example 18: 1-(Piperdin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-trifluoromethylphenyl)-amino]pyrimidin-4-yl)imidazole

Example 19: 1-(Piperdin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-4,difluorophenyl)-amino]pyrimidin-4-yl)imidazole

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed Is:

Claim 1. A process of making compounds of Formula (I)



(I)

wherein

R_1 is an optionally substituted pyrimidin-4-yl ring;

R_4 is an optionally substituted phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl ring;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

R_2 is $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl,

$(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, $-C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

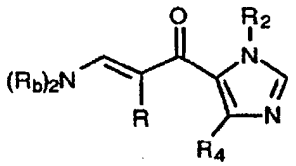
R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl; and

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

which process comprises:

a) reacting a compound of the formula



(VIII)

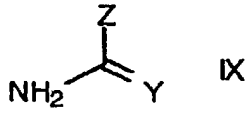
wherein

R_b is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl, all of which may be optionally substituted;

R is a substituent group on the R_1 moiety as defined for Formula (I), or is an optionally substituted alkyl or aryl group; and

R_2 and R_4 are defined as for Formula (I);

with a compound of the formula



IX

wherein

Z is $N(R^d)_2$, SR^e, OR^e, or R^d.

R^d is independently hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl, all of which may be optionally substituted;

R^e is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl, all of which may be optionally substituted; and

Y is O, S, or NH;

to yield a compound of Formula (I), or pharmaceutically acceptable salt thereof.

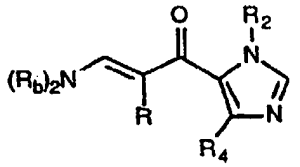
2. The process according to Claim 1 wherein the reaction is at a temperature of about 25°C to about 110°C.

3. The process according to Claim 1 wherein the reaction uses a solvent which is an alcohol, toluene, DMF, DMSO or mixtures thereof.

4. The process according to Claim 1 wherein the Y is Formula (IX) is NH.

5. The process according to Claim 1 wherein the reaction uses a bases which is NaOMe, NaOEt, potassium carbonate, or potassium hydroxide.

6. A compound of the formula:



(VIII)

wherein

R_b is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl, all of which may be optionally substituted;

R is optionally substituted alkyl, optionally substituted aryl, halogen, hydroxyl, thiol, C_{1-10} 4 alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, CH_2OR_{12}, amino, mono or di-C_{1-10} alkyl substituted amino, NHR_{21}, $N(R_{10})C(O)R_a$ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_4 is an optionally substituted phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl ring;

R_2 is -$(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10

n' is 0, or an integer having a value of 1 to 10;

m' is an integer having a value of 1 or 2,

Z is oxygen or sulfur;

R_9 is hydrogen, -$C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

R_{15} is R_{10} or $C(Z)$-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl;

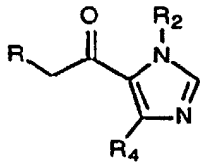
R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

R_{21} is alkyl, aryl, arylC_{1-6}alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6}alkyl, wherein each of these moieties may be optionally substituted.

7. The compound according to Claim 6 wherein R_4 is 4-fluorophenyl, and R_2 is an optionally substituted heterocyclic, C_{1-10} alkyl, C_{3-7} cycloalkyl, or C_{3-7} cycloalkyl C_{1-10} alkyl.

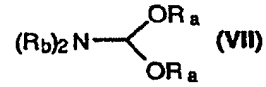
8. The compound according to Claim 7 wherein R is C_{1-4} alkoxy, C_{1-4} alkyl thio, or amino.

9. The process according to Claim 1 wherein a compound of Formula (VIII) is produced by reacting a compound of the formula



(VI)

wherein R, R_2 and R_4 are defined above;
with a compound the formula



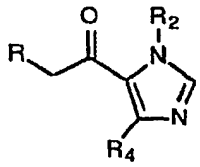
(VII)

wherein R_a is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl, all of which may be optionally substituted; and
R_b is alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, arylalkyl, heteroarylalkyl, heterocylic, or heterocyclicalkyl, all of which maybe optionally substituted;
to yield a compound of Formula (VIII).

10. The process according to Claim 9 wherein the compounds are heated with dimethylformamide dimethyl , tri(dimethylamino)methane, tert-butoxybis-dimethylamino)methane, or any suitable enaminating agent, optionally in the presence of a solvent.

11. The process according to Claim 10 wherein the optional solvents are toluene ethanol, 1-propanol, 2-propanol, DMF or DMSO, or mixtures thereof.

12. A compound of the formula


(VI)

wherein

R is optionally substituted C_{1-10} alkyl, optionally substituted aryl, halogen, hydroxyl, thiol, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, CH_2OR_{12}, amino, mono or di-C_{1-10} alkyl substituted amino, NHR_{21}, $N(R_{10})C(O)R_a$ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_4 is an optionally substituted phenyl, naphth-1-yl or naphth-2-yl, or heteroaryl ring;

R_2 is $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10

n' is 0, or an integer having a value of 1 to 10;

m' is an integer having a value of 1 or 2,

Z is oxygen or sulfur;

R_9 is hydrogen, $-C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9;

R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl;

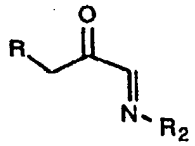
R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl; and

R_{21} is alkyl, aryl, arylC_{1-6}alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6}alkyl, wherein each of these moieties may be optionally substituted.

13. The compound according to Claim 12 wherein R_4 is 4-fluorophenyl, and R_2 is an optionally substituted heterocyclic, C_{1-10} alkyl, C_{3-7} cycloalkyl, or C_{3-7} cycloalkyl C_{1-10} alkyl.

14. The compound according to Claim 13 wherein R is C_{1-4} alkoxy, C_{1-4} alkyl thio, or amino.

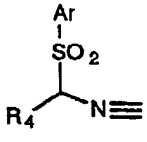
15. A process according to Claim 9 wherein a compound of Formula VI is prepared by reacting a compound of the formula



(IV)

wherein R and R_2 are as defined in Formula (I),

with a compound of Formula (V) and a suitable base,

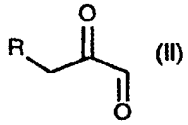


(V)

wherein Ar is an optionally substituted aryl; and R_4 is as defined for Formula (I); to yield a compound of Formula (VI).

16. The process according to Claim 15 wherein the imine of Formula (IV) is prepared in situ, followed by reaction with a compound of Formula (V).

17. The process according to Claim 16 wherein the imine is formed by reacting a compound of formula (II), as defined below



(II)

wherein R is as defined for according to Claim 1, with a compound of formula (III)

$$R_2NH_2 \quad \text{(III)}$$

wherein R_2 is defined as for Formula (I).

18. The process according to Claim 16 wherein the imine formation uses a solvent of THF, MeCN, toluene, EtOAc, DMF, DMSO or mixtures thereof.

19. The process according to Claim 16 wherein the imine formation utilizes a temperature from about 0°C to about 65°C.

20. The process according to Claim 16 wherein the reaction may optionally include a base which is potassium carbonate, sodium carbonate, K_3PO_4, K_2HPO_4, Na_2HPO_4, secondary and tertiary amine bases, or tetramethyl guanidine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20599

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 401/14
US CL :544/331
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/331

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2,748,119 A (EVANSTON, III) 29 May 1956 (29.05.56), see entire document, especially column 1.	1-20 (parts)
A	US 3,557,114 A (BICKING) 19 January 1971 (19.01.71), see entire document, especially column 1.	1-20 (parts)

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 FEBRUARY 1997	Date of mailing of the international search report 13 MAR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer R.W. RAMSUER aco Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20599

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-20, parts
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20599

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. R1, R2, R3, R4, R6, Rb, R, Ar, Y, Z, etc.) and the many processes) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains an imidazole ring which does not define a contribution over the prior art. Therefore, the first discernable invention as found in Example 4 (i.e. the reaction of 1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5(3-N, N dimethylamino-trans-1-propenone) imidazole with N-methylguonidine. HCl to prepare 1-(1-Ethoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-(methylamino)-4-pyrimidinyl) imidazole, has been searched.